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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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tone is low (Marshall *et al.*, 1987; Hanel and Lands, 1982). Further, acetaminophen does not inhibit neutrophil activation as do other NSAIDs (Abramson and Weissmann, 1989).

Single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular and respiratory systems. Acid–base changes do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Acetaminophen has no effects on platelets, bleeding time, or the excretion of uric acid.

Pharmacokinetics and Metabolism. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90% to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P450–mediated *N*-hydroxylation to form *N*-acetyl-benzoquinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after ingestion of large doses of acetaminophen, the metabolite is formed in amounts sufficient to deplete hepatic glutathione (*see* below).

Therapeutic Uses. Acetaminophen is a suitable substitute for aspirin for analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (*e.g.*, those with peptic ulcer) or when the prolongation of bleeding time caused by aspirin would be a disadvantage. The conventional oral dose of acetaminophen is 325 to 1000 mg (650 mg rectally); the total daily dose should not exceed 4000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg also may be used.

Toxic Effects. In recommended therapeutic dosage, acetaminophen usually is well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to acetaminophen. In a few isolated cases, the use of acetaminophen has been associated with neutropenia, thrombocytopenia, and pancytopenia.

The most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis (*see* Thomas, 1993). Renal tubular necrosis and hypoglycemic coma also may occur. The mechanism by which overdosage with acetaminophen leads to hepatocellular injury and death involves its conversion to a toxic reactive metabolite (*see also* Chapter 4). Minor pathways of acetaminophen elimination are *via* conjugation with glucuronide and sulfate. The major pathway of metabolism is *via* cytochrome P450s to the intermediate, *N*-acetyl-*para*-benzoquinonimine, which is very electrophilic. Under normal circumstances, this intermediate is inated by conjugation with glutathione (GSH) and then metabolized to a mercapturic acid and excreted into the However, in the setting of acetaminophen overdose, hepatic lular levels of GSH become depleted. Two consequences as result of depletion of GSH. Since GSH is an important in antioxidant defense, hepatocytes are rendered highly susble to oxidant injury. Depletion of GSH also allows the intermediate to bind covalently to cell macromolecules to dysfunction of enzymatic systems.

Hepatotoxicity. In adults, hepatotoxicity may occur ingestion of a single dose of 10 to 15 g (150 to 250 mg acetaminophen; doses of 20 to 25 g or more are potentially fatal. Alcoholics can have hepatotoxicity with much lower even with doses in the therapeutic range. The mechanism this effect is discussed above (*see also* Chapter 4). Symptoms that occur during the first 2 days of acute poisoning by aminophen may not reflect the potential seriousness of the ication. Nausea, vomiting, anorexia, diaphoresis, and abdominal pain occur during the initial 24 hours and may persist a week or more. Clinical indications of hepatic damage usually manifest within 2 to 4 days of ingestion of toxic doses. aminotransferases are elevated (sometimes markedly), the concentration of bilirubin in plasma may be increased addition, the prothrombin time is prolonged. Perhaps 90% poisoned patients who do not receive specific treatment have severe liver damage; of these, 10% to 20% eventually die hepatic failure. Acute renal failure also occurs in some patients. Biopsy of the liver reveals centrilobular necrosis with sparing of the periportal area. In nonfatal cases, the hepatic lesion reversible over a period of weeks or months.

Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1000 IU per liter of plasma) occurs 90% of patients with plasma concentrations of acetaminophen greater than 300 μg/ml at 4 hours or 45 μg/ml at 15 hours after the ingestion of the drug. Minimal hepatic damage is anticipated when the drug concentration is less than 120 μg/ml at 4 hours or 30 μg/ml at 12 hours after ingestion. The potential severity of hepatic necrosis also can be predicted from the half-life of acetaminophen observed in the patient; values greater than 4 hours imply that necrosis will occur, while those greater than 12 hours suggest that hepatic coma is likely. A nomogram provided in Figure 27–2 relates the plasma level of acetaminophen and time after ingestion to the predicted severity of liver injury (*see* Rumack *et al.*, 1981).

Early diagnosis is vital in the treatment of overdosage with acetaminophen, and methods are available for the rapid determination of concentrations of the drug in plasma. However, therapy should not be delayed while awaiting laboratory results if a history suggests a significant overdosage. Vigorous supportive therapy is essential when intoxication is severe. Gastric lavage should be performed in all cases, preferably within 4 hours of the ingestion.

The principal antidotal treatment is the administration of sulfhydryl compounds, which probably act, in part, by replenishing hepatic stores of glutathione. *N-acetylcysteine* (MUCOMYST, MUCOSIL) is effective when given orally or intravenously. An intravenous form is available in Europe, where it is considered the treatment of choice. When given orally, the *N*-acetylcysteine solution (which has a foul smell and taste) is diluted with

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Table A–II–1
PHARMACOKINETIC DATA

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
ABACAVIR[a] (Chapter 51)							
83 (63–110)	1 (0–4)	—	12.8 (9.3–17.5)	0.84 (0.69–1.03)	1.0 (0.8–1.3)	Tab: 0.63 (0.4–1.1)[b] Sol: 0.5 (0.5–0.6)[b]	Tab: 2.6 (2.3–2.9) $\mu g/ml$[b] Sol: 2.9 (2.5–3.4) $\mu g/ml$[b]
ACETAMINOPHEN[a] (Chapter 27)							
88 ± 15 ⟷ Child	3 ± 1 ⟷ Neo, Child	<20	5.0 ± 1.4[b] ↓ Hep[c] ⟷ Aged, Child ↑ Obes, HTh, Preg	0.95 ± 0.12[b] ⟷ Aged, Hep[c] LTh, HTh, Child	2.0 ± 0.4 ⟷ RD, Obes, Child ↑ Neo, Hep[c] ↓ HTh, Preg	0.33–1.4[d]	20 $\mu g/ml$[e]
(L)-α-ACETYL-METHADOL (LAAM)[a] (Chapter 23)							
47 ± 5	6	80	4.93 ± 0.58	7.0	L: 18.5 ± 4.9 NL: 23.9 ± 3.2 DL: 65.8 ± 10.1	L: 2.6 ± 0.2[b] NL: 3.9 ± 0.7[b] DL: 31 ± 9.6[b]	L: 63 ± 8 ng/ml[b] NL: 44 ± 4 ng/ml[b] DL: 19 ± 1 ng/ml[b]
ACETYLSALICYLIC ACID[a] (Chapters 27, 55)							
68 ± 3 ⟷ Aged, Cir	1.4 ± 1.2	49 ↓ RD	9.3 ± 1.1 ⟷ Aged, Cir	0.15 ± 0.03	0.25 ± 0.03 ⟷ Hep	0.39 ± 0.21[b]	24 ± 4 $\mu g/ml$[b]

[a]Data from male subjects with HIV infection. Values are geometric means and 95% CI. Metabolized by ADH, UGT, and other enzymes.
[b]C_{max} and T_{max} (geometric mean and 95% CI) following a 300-mg oral tablet (Tab) or solution (Sol).

References: Barry, M., Mulcahy, F., Merry, C., Gibbons, S., and Back, D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin. Pharmacokinet.*, 1999, *36*:289–304.
Chittick, G.E., Gillotin, C., McDowell, J.A., Lou, Y., Edwards, K.D., Prince, W.T., and Stein, D.S. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. *Pharmacotherapy*, 1999, *19*:932–942.

[a]Values reported are for a linear kinetic model for doses less than 2 g; drug exhibits concentration-dependent kinetics above this dose.
[b]Assuming a 70-kg body weight; reported range, 65 to 72 kg.
[c]Acetaminophen-induced hepatic damage or acute viral hepatitis.
[d]Absorption rate, but not extent, depends on gastric emptying; hence, slowed after food as well as in some disease states and cotreatment with drugs that cause gastroparesis.
[e]Mean concentration following a 20-mg/kg oral dose. Hepatic toxicity associated with levels >300 $\mu g/ml$ at 4 hours after an overdose.

Reference: Forrest, J.A., Clements, J.A., and Prescott, L.F. Clinical pharmacokinetics of paracetamol. *Clin. Pharmacokinet.*, 1982, 7:93–107.

[a]Data from healthy adult male subjects. LAAM (L) is metabolized by cytochrome P450 (primarily CYP3A) to active metabolites, nor-LAAM (NL) and dinor-LAAM (DL).
[b]Following a single 40-mg oral dose.

References: Kaiko, R.F., Chatterjie, N., and Imondi, C.E. Simultaneous determination of acetylmethadol and its active biotransformation products in human biofluids. *J. Chromatogr.*, 1975, *109*: 247–258.
Walsh, S.L., Johnson, R.E., Cone, E.J., and Bigelow, G.E. Intravenous and oral *l*-α-acetylmethadol: pharmacodynamics and pharmacokinetics in humans. *J. Pharmacol. Exp. Ther.*, 1998, *285*:71–82.

[a]Values given are for unchanged parent drug. Acetylsalicylic acid is converted to salicylic acid during and after absorption (CL and $t_{1/2}$ of salicylate are dose-dependent; half-life varies between 2–6 hours after a 300-mg dose to 15 hours when there is intoxication).
[b]Total drug given to adults.

Reference: Roberts, M.S., Rumble, R.H., Wanwimolruk, S., Thomas, D., and Brooks, P.M. Pharmacokinetics of aspirin and salicylate in elderly subjects and in patients with alcoholic liver disease. *Eur. J. Clin. Pharmacol.*, 1983, *25*:253–261.

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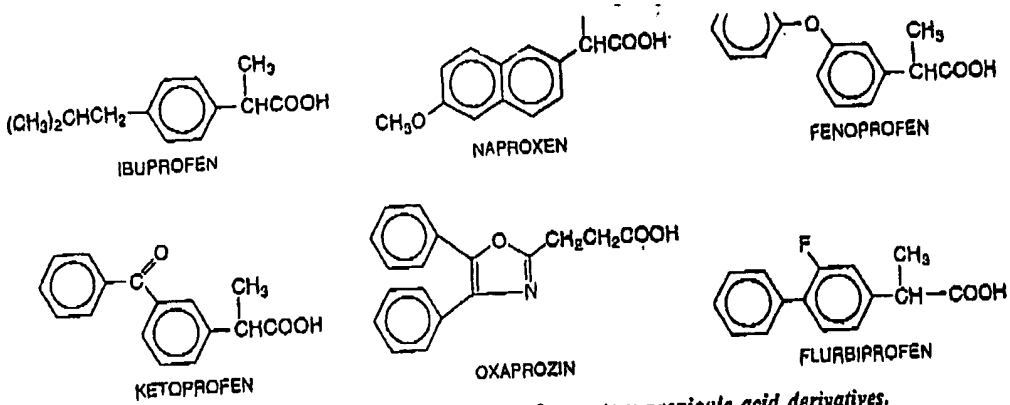

Figure 27–3. Structural formulas of antiinflammatory propionic acid derivatives.

ith this drug is greater. It is available for sale without a prescription in the United States. Naproxen has a longer half-life than most of the other structurally and functionally similar agents, making twice-daily administration of it feasible. This drug also is available without prescription in the United States. Oxaprozin also has a long half-life and can be given once daily. The structural formulas of these drugs are shown in Figure 27–3.

Pharmacological Properties. The pharmacodynamic properties of the propionic acid derivatives do not differ significantly. All are effective cyclooxygenase inhibitors, although there is considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenoprofen, and aspirin are roughly equipotent as cyclooxygenase inhibitors. All of these agents alter platelet function and prolong bleeding time, and it should be assumed that any patient who is intolerant of aspirin also will experience a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on leukocyte function; naproxen is particularly potent in this regard. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental animal models of inflammation; all have useful antiinflammatory, analgesic, and antipyretic activities in human beings. Although all of these compounds can cause gastric toxicity in patients, these are usually less severe than with aspirin.

It is difficult to find data on which to base a rational choice among the members of the propionic acid derivatives, if in fact one can be made. However, in relatively small clinical studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (*see* Huskisson, *in* Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenoprofen. There was considerable interpatient variation in the preference for a single drug and also between the designations of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis probably will achieve adequate symptomatic relief from the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

Drug Interactions. The potential adverse drug interactions of particular concern with propionic acid derivatives result from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

Ibuprofen

Ibuprofen is supplied as tablets containing 200 to 800 mg; only the 200-mg tablets (ADVIL, NUPRIN, others) are available without a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses up to 3200 mg in divided portions may be given, although the usual total dose is 1200 to 1800 mg. It also may be possible to reduce the dosage for maintenance purposes. For mild to moderate pain, especially that of primary dysmenorrhea, the usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. Ibuprofen has been discussed in detail by Kantor (1979) and by Adams and Buckler (*in* Symposium, 1983a).

Pharmacokinetics and Metabolism. Ibuprofen is rapidly absorbed after oral administration, and peak concentration

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Table A–II–1
PHARMACOKINETIC DATA (*Continued*)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
HYDROMORPHONE[a] (Chapter 23)							
Oral: 42 ± 23 SC: ~80	6	7.1	14.6 ± 7.6	2.90 ± 1.31[b]	2.4 ± 0.6	IV: –[c] Oral: 1.1 ± 0.2[c]	IV: 242 ng/ml[c] Oral: 11.8 ± 2.6 ng/ml[c]
HYDROXYUREA[a,2] (Chapter 52)							
108 ± 18 (79–108)	35.8 ± 14.2	Negligible	72 ± 17 ml · min^{-1} (m^2)$^{-1}$[b] (36.2–72.3)	19.7 ± 4.6 l/m^2	3.4 ± 0.7 (2.8–4.5)	IV: 0.5[c] Oral: 1.2 ± 1.2[c]	IV: 1007 ± 371 μM[c] Oral: 794 ± 241 μM[c]
IBUPROFEN[a] (Chapter 27)							
~80	<1	>99[b] ⟷ RA, Alb	0.75 ± 0.20[b,c] ↑ CF ⟷ Child, RA	0.15 ± 0.02[c] ↑ CF	2 ± 0.5[b] ⟷ RA, CF, Child ↑ Cirr	1.6 ± 0.3[d]	61.1 ± 5.5 μg/ml[d]

[a]Data from healthy male subjects. Extensively metabolized. The principal metabolite, 3-glucuronide, accumulates to much higher (27-fold) levels than parent drug, and may contribute to some side effects (not antinociceptive).
[b]V_{area} reported.
[c]Following a single 2-mg IV (bolus, sample at 3 minutes) or 4-mg oral dose.

References: Hagen, N., Thirlwell, M.P., Dhaliwal, H.S., Babul, N., Harsanyi, Z., and Darke, A.C. Steady-state pharmacokinetics of hydromorphone and hydromorphone-3-glucuronide in cancer patients after immediate and controlled-release hydromorphone. *J. Clin. Pharmacol.*, 1995, *35*:37–44.

Moulin, D.E., Kreeft, J.H., Murray-Parsons, N., and Bouquillon, A.I. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet*, 1991, *337*:465–468.

Parab, P.V., Ritschel, W.A., Coyle, D.E., Gregg, R.V., and Denson, D.D. Pharmacokinetics of hydromorphone after intravenous, perioral and rectal administration to human subjects. *Biopharm. Drug Dispos.*, 1988, *9*:183–199.

[a]Data from male and female patients treated for solid tumors. A range of mean values from multiple studies is shown in parenthesis.
[b]Nonrenal elimination of hydroxyurea is thought to exhibit saturable kinetics through a 10- to 30-mg/kg dose range.
[c]Following a single 2-g, 30-minute intravenous infusion or oral dose.

References: Gwilt, P.R., and Tracewell, W.G. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin. Pharmacokinet.*, 1998, *34*:347–358.

Rodriguez, G.I., Kuhn, J.G., Weiss, G.R., Hilsenbeck, S.G., Eckardt, J.R., Thurman, A., Rinaldi, D.A., Hodges, S., Von Hoff, D.D., and Rowinsky E.K. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. *Blood*, 1998, *91*:1533–1541.

[a]Racemic mixture. Kinetic parameters for the active *S*-(+)-enantiomer do not differ from those for the inactive *R*-(–)-enantiomer when administered separately; 63 ± 6% of the *R*-(–)-enantiomer undergoes inversion to the active isomer.
[b]Unbound percent of *S*-(+)-ibuprofen (0.77 ± 0.20%) is significantly greater than that of *R*-(–)-ibuprofen (0.45 ± 0.06%). Binding of each enantiomer is concentration dependent and is influenced by the presence of the optical antipode, leading to nonlinear elimination kinetics.
[c]*CL/F* and *V*$_d$*/F* reported.
[d]Following a single 800-mg dose of racemate. A level of 10 μg/ml provides antipyresis in febrile children.

References: Lee, E.J., Williams, K., Day, R., Graham, G., and Champion, D. Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.*, 1985, *19*:669–674.

Lockwood, G.F., Albert, K.S., Gillespie, W.R., Bole, G.G., Harkcom, T.M., Spooner, G.J., and Wagner, J.G. Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. *Clin. Pharmacol. Ther.*, 1983, *34*:97–103.

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